04-20-00

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: U.S. Patent No. 4,911,920
07/154514
Issued: March 27, 1990

EXPRESS MAILING LABEL NO. EL534529609US

Assignee: Alcon Laboratories, Inc.

Attention: BOX PATENT EXTENSION

TRANSMITTAL OF FEE UNDER 37 C.F.R. §1.20(j)

Box Patent Extension
Assistant Commissioner of Patents
Washington, D. C. 20231

Dear Sir:

An application for extension of the term of the above-identified patent has been filed herewith. Please charge the $1,120.00 fee required under 37. C.F.R. §§1.740(a)(14) and 1.20(j) to Deposit Account No. 01-0682. The Commissioner is hereby authorized to charge any additional fees which may be required. A duplicate of this paper is attached.

Respectfully submitted,
ALCON LABORATORIES, INC.

Date: April 19, 2000

By: Sally Yeager
Sally Yeager
Registration No. Reg. 32,757

Address for Correspondence:

Sally Yeager - (Q-148)
Patent Department
Alcon Laboratories, Inc.
6201 So. Freeway
Fort Worth, TX 76134-2099
(817) 551-4031

Attorney Docket No.: 902B-2

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Express Mailing Label No. EL534529609US

Issued: March 27, 1990

Assignee: Alcon Laboratories, Inc.

Attention: Box Patent Extension

APPLICATION FOR EXTENSION OF TERM UNDER 35 U.S.C. §156

Box Patent Extension
Assistant Commissioner of Patents
Washington, D.C. 20231

Dear Sir:

Alcon Laboratories, Inc. ("Alcon") hereby applies for extension of the term of United States Patent No. 4,911,920.

BACKGROUND

Alcon is the owner of United States Patent No. 4,911,920 (sometimes referred to herein as the '920 patent). Photocopies of the Assignment and Notice of Recordation are attached as Appendix A. The '920 patent is owned by Alcon Laboratories, Inc. a wholly owned subsidiary of Alcon Universal Ltd., the owner of the NDA for Betaxon™ as discussed in the following pages.

The '920 patent is directed to compositions and methods for lowering and controlling intraocular pressure. Claims 1-12 include the active ingredient, betaxolol, which includes levobetaxolol.

Levobetaxolol is the active ingredient of a new ophthalmic pharmaceutical product developed by Alcon. That product is known as BETAXON™ (levobetaxolol hydrochloride ophthalmic suspension) 0.5% as base. The United States Food and Drug Administration (FDA) granted Alcon's application for approval to market this product on February 23, 2000. The product is referred to hereinafter as "the approved product."

As explained below, it is believed that the '920 patent is eligible for an extension of term under the provision of 35 U.S.C. §156. Alcon has therefore submitted this Application for Extension of Term in accordance with 35 U.S.C. §156 and the applicable Patent Office regulations (i.e., 37 C.F.R. §§ 1.710, et. seq.).

ELIGIBILITY

United States Patent No. 4,911,920 is eligible for extension under the provisions of 35 U.S.C. §156(a) and 37 C.F.R. §§1.710 and 1.720. The criteria for eligibility are set forth below:

(1) the '920 patent claims, among other things, a method for using the approved product to treat elevated intraocular pressure;

(2) the term of the '920 patent has not expired prior to submission of this Application;

(3) the term of the '920 patent has never been previously extended;

(4) no other patent has been extended based on the regulatory review period for the approved product;

(5) the approved product has been subject to a regulatory review period of the type defined in 35 U.S.C. §156(g)(1)(A);

(6) the permission for commercial marketing or use of the approved product resulting from the regulatory review period is the first permitted commercial marketing or use of any human drug product containing the active ingredient contained in the approved product (i.e., levobetaxolol); and

(7) an application for extension of term meeting the requirements of 35 U.S.C. §156(d) has been submitted within the period specified in 35 U.S.C. §156(d)(1).

APPLICATION

In accordance with the requirements of 35 U.S.C. §156(d) and 37 C.F.R. §§ 1.730 and 1.740, Alcon presents the following information. The paragraph numbers utilized below correspond to the paragraph numbers under subparagraph (a) of 37 C.F.R. §1.740:

(1) The approved product is a sterile ophthalmic suspension which contains levobetaxolol (0.5%) as its sole active ingredient.

Further details concerning this compound are presented in the USP Dictionary of USAN and International Drug Names; a copy of page 415 of that publication is attached as Appendix B. Further details concerning the approved product are

presented in the FDA-approved package insert; a copy of that insert is attached as Appendix C.

(2) The regulatory review occurred under Sections 505(i) and 505(b) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301 et. seq.)

(3) The approved product received FDA approval under Section 505(b) of the Federal Food, Drug, and Cosmetic Act on February 23, 2000. A copy of the approval letter is attached as Appendix D.

(4) As stated above, the active ingredient of the approved product is levobetaxolol. This compound has not been previously approved for commercial marketing or use under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act.

(5) This Application is being submitted within the sixty (60) day period specified in 35 U.S.C. §156(d)(1) and 37 C.F.R. §1.720(f), which period expires on April 23, 2000.

(6) The patent for which an extension is being sought is United States Patent No. 4,911,920. This patent was issued to Rajni Jani and Robert G. Harris on March 27, 1990, and will expire on March 27, 2007.

(7) A copy of United States Patent No. 4,911,920 in the form of a

cut-up copy wherein only a single column is reproduced on each page is attached as Appendix E.

(8) The first maintenance fee was mailed on July 7, 1993, and a second on June 30, 1997. A copy of the Maintenance Fee Transmittal Forms, Return Cards, and the Statements are attached as Appendix F.

(9) United States Patent No. 4,911,920 claims formulations for controlling intraocular pressure comprising levobetaxolol, and a method for controlling intraocular pressure with levobetaxolol. Levobetaxolol is the active ingredient of the approved product. As indicated in the package insert (see Appendix C, page 4), the approved product is indicated for lowering intraocular pressure in patients with chronic open angle glaucoma or ocular hypertension.

The use of the approved product to treat intraocular pressure is specifically set forth in Claim 7 of the '920 patent. Claim 7 reads as follows:

> 7. A method of treatment for controlling and lowering intraocular pressure which comprises administering topically to the affected eye a pharmaceutical composition which includes: a therapeutically effective amount of betaxolol; an amount of an anionic

mucomimetic polymer having carboxylic acid functional groups which comprise from 2 to 7 carbon atoms per functional group and a molecular weight of from 50,000 to 6 million such that the composition in the form of an aqueous gel or pourable aqueous dispersion has a viscosity of about 1 to 20,000 cps.; and sodium poly(styrene-divinylbenzene) sulfonic acid at a concentration of from about 0.05% to 10.0% by weight, the composition having a pH of from about 3.0 to 8.5.

RELEVANT DATES AND INFORMATION PURSUANT TO 35 U.S.C. §156(g)

(10) The relevant dates and information specified in 35 U.S.C. §156(g) are as follows:

(a) IND 53,513

The investigational new drug ("IND") application was filed on June 23, 1997. The IND application was assigned serial number 53,513.

(b) NDA 21-114

The new drug application ("NDA") was submitted on August 25, 1999. The NDA was assigned serial number 21-114. The NDA was approved February 23, 2000.

BRIEF DESCRIPTION OF ACTIVITIES DURING THE REGULATORY REVIEW PERIOD

(11) The activities undertaken by Alcon during the regulatory review periods identified in paragraph (1) above were as follows:

(a) 06/23/97 – 06/23/98

Investigational new Drug application No. 53,513 (hereinafter "IND") was submitted to the FDA under Section 505(i) of the Federal Food, Drug and Cosmetic Act on June 23, 1997. A Phase II clinical safety dose response study was then initiated on August 2, 1997. In addition, with this clinical study and additional clinical studies, informational and protocol amendments were submitted to the FDA in July and August of 1997, and February, March, April, and May of 1998. A meeting with the FDA was held on January 20, 1998, to discuss our Phase III clinical plan and the design of these clinical studies. Minutes to this meeting issued June 23, 1998. Phase III protocols to study the safety and efficacy of levobetaxolol in glaucoma patients were filed to the IND in February, March, and April, 1998, and the studies immediately initiated. In addition, amendments were filed in support of these protocols in April and May 1999.

(b) 06/23/98 – 06/23/99

Annual Progress Report No. 1 was submitted to

the FDA. Informational and protocol amendments were submitted to the FDA in June, August, September, and December, 1998. In November 1998, a study was initiated to demonstrate superiority of levobetaxolol 0.5% to Timolol 0.5% in its effect on FEV patients with reactive airway disease. In December 1998, two clinical studies were initiated, (1) to characterize the steady-state pharmacokinetics following topical ocular administration to normal volunteers and (2) to compare cardiovascular effects during exercise in normal subjects age 60 and over. In March 1999, a Pre-NDA meeting was requested in order to review the content and format of the NDA with the FDA. A briefing packet was provided to the FDA in April and the Meeting was held in May. Meeting minutes were issued on May 10. On May 25, 1999, the Chemistry, Manufacturing & Controls and the Microbiology Sections of the New Drug application No. 21-114 (hereinafter "NDA") was submitted to the FDA. On June 15, 1999, FDA was notified that sponsorship of the IND was being transferred from Alcon Laboratories, Inc. to Alcon Universal Ltd. (Alcon Laboratories, Inc. is a wholly owned subsidiary of Alcon Universal Ltd.)

(c) 06/23/99 - Present

On August 25, the remaining sections of the NDA were filed. Amendments to the NDA and responses to FDA reviewers' requests were submitted in October, November, and December 1999, and in January and February 2000. In January the four-month Safety Update including the

preliminary study report for the long-term safety study was filed with the FDA. The NDA was approved on February 23, 2000.

(d) Summary

The testing phase, beginning July of 1997, was characterized by continuous and uninterrupted clinical safety and efficacy studies through the time of NDA filing on August 25, 1999. Subsequent to the NDA filing, Alcon continuously and diligently sought approval of its NDA covering the approved product. There were no periods between June 23, 1997 and February 23, 2000, during which Alcon did not actively pursue approval from the FDA for commercial marketing of the approved product.

STATEMENT OF APPLICANT'S OPINION CONCERNING ELIGIBILITY FOR AN EXTENSION AND THE LENGTH OF THE EXTENSION

(12) In the opinion of Alcon, United States Patent No. 4,911,920 is eligible for an extension of 579 days. The length of the extension was calculated as follows:

(a) IND Period

The IND period began on June 23, 1997, and ended August 24, 1999. The IND period therefore included a total of 793 days. The '920 patent issued on March 27, 1990, 0 days after the IND period began. Therefore the IND period for calculation purposes is 793 days (i.e., 793 days minus 0 days). One-half of this total is 396 days.

(b) NDA Period

The NDA period began on August 25, 1999, and ended on April 23, 2000. The NDA period therefore included a total of 183 days.

(c) Length of Extension

The regulatory review period for purposes of patent term extension was 579 days (i.e., 396 days plus 183

days).

(d) Limitation on Extension

Under the provision of 35 U.S.C. §156(c)(3), the term of a patent remaining after the date of product approval cannot exceed fourteen years. In the present case, this means that the term of the '902 patent cannot be extended beyond February 23, 2014. It is the opinion of Applicant that the entire 579 days available for patent extension may be utilized.

(13) Alcon hereby acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension requested herein.

(14) The accompanying Transmittal Letter requests that the $1,120.00 fee required by 37 C.F.R. §1.20(j) be charged to Deposit Account No. 01-0682.

(15) Alcon requests that all correspondence and inquiries in connection with this Application be directed to the following individual:

Sally S. Yeager
R&D Counsel, Q-148
Alcon Laboratories, Inc.
6201 South Freeway
Fort Worth, Texas 76134

Phone: (817) 551-4031
Fax: (817) 551-4610

(16) A certified duplicate of this Application is being filed herewith.

(17) A Declaration meeting the requirements of 37 C.F.R. §1.740(b) is attached.

Based on the foregoing, it is believed that United States Patent No. 4,911,920 is entitled to an extension of 579 days. An official notice to that effect in the form of a certificate of extension is respectfully requested.

Respectfully submitted,

ALCON LABORATORIES, INC.

Date April 19, 2000

By _____
Sally Yeager
Registration No. 32,757

Address for Correspondence:
Sally Yeager
Patent Department, Q-148
Alcon Laboratories, Inc.
6201 South Freeway
Fort Worth, Texas 76134
Phone: (817) 551-4031

Docket No. 902B-2

APPENDIX A

Assignment and Recordation Sheet

TO: LOWE, KING, PRICE & BECKER
2001 JEFF. DAVIS HWY.
ARLINGTON, VA 22202

UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT DIVISION OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS AVAILABLE AT THE U.S. PATENT AND TRADEMARK OFFICE ON THE REEL AND FRAME NUMBER REFERENCED BELOW. A DIGEST OF THE DOCUMENT HAS ALSO BEEN MADE AND APPEARS IN THE OFFICE'S RECORDS AS SHOWN:

ASSIGNOR: 001 JANI, RAJNI DOC DATE: 10/25/84
ASSIGNEE: 002 HARRIS, ROBERT G. DOC DATE: 10/25/84

RECORDATION DATE: 10/31/84 NUMBER OF PAGES 002 REEL/FRAME 4331/0580

DIGEST: ASSIGNMENT OF ASSIGNORS INTEREST

ASSIGNEE: 501 ALCON LABORATORIES, INC. 6201 SOUTH FREEWAY, P.O. BOX 195
9 FORT WORTH, TX 76101 A CORP. OF DE

SERIAL NUMBER 6-667003 FILING DATE 10/31/84
PATENT NUMBER ISSUE DATE 00/00/00

TITLE OF INVENTION: SUSTAINED RELEASE, COMFORT FORMULATION FOR GLAUCOMA THERAPY

INVENTOR: 001 JANI, RAJNI
INVENTOR: 002 HARRIS, ROBERT G.

A S S I G N M E N T

WHEREAS I am a below named inventor of the invention set forth in an application for United States Letters Patent executed by me the 25th day of October, 1984, entitled

"SUSTAINED RELEASE, COMFORT FORMULATION FOR GLAUCOMA THERAPY",

filed concurrently herewith;

AND WHEREAS, ALCON LABORATORIES, INC., a corporation of the State of Delaware and having a place of business at 6201 South Freeway, P. O. Box 1959, Fort Worth, Texas 76101, is desirous of acquiring the entire right, title and interest in and to said invention and in and to any and all Letters Patent of the United States and foreign countries which may be obtained therefor;

NOW, THEREFORE, for good and valuable consideration, I do hereby sell, assign and transfer to ALCON LABORATORIES, INC., its legal representatives, successors, and assigns, the entire right, title and interest in and to said invention as set forth in the above-mentioned application, and in and to any and all patents of the United States and foreign countries which may be issued for said invention;

UPON SAID CONSIDERATIONS, I hereby agree that I will not execute any writing or do any act whatsoever conflicting with these presents, and that I will, at any time upon request, without further or additional consideration but at the expense of said assignee, execute such additional assignments and other writings and do such additional acts as said assignee may deem necessary or desirable to perfect the assignee's enjoyment of this grant, and render all necessary assistance in making application for and obtaining original, divisional, reexamined, reissued, or other Letters Patent of the United States or of any and all foreign countries on said invention, and in enforcing any rights in action accruing as a result of such applications or patents, said assistance to include my cooperation in all prosecution associated with obtaining such applications or patents and my provision of testimony in any proceedings or transactions involving such applications or patents, it being understood that the foregoing covenant and agreement shall bind, and inure to the benefit of, the assigns and legal representatives of assignor and assignee;

AND I request the Commissioner of Patents and Trademarks to issue any Letters Patent of the United States which may be issued for said invention to said ALCON LABORATORIES, INC., its legal representatives, successors or assigns, as the sole owner of the entire right, title and interest in said patent and the invention covered thereby.

Full name of joint inventor: Rajni Jani

Address: 3753 Misty Meadow Drive

Fort Worth, Texas 76133

Inventor's signature: Rajni Jani

Date: October 25, 1984

Full name of joint inventor: Robert Gregg Harris

Address: 3224 Westcliff Road W.

Fort Worth, Texas 76109

RECORDED
PATENT & TRADEMARK OFFICE
OCT 31 1984
COMMISSIONER OF PATENTS

Inventor's signature: Robert Gregg Harris

Date: October 25, 1984

STATE OF TEXAS)
COUNTY OF TARRANT)

On this 25 day of October, 1984, before me personally appeared RAJNI JANI and ROBERT GREGG HARRIS, to me known to be the persons named in and who executed the above instrument, and acknowledged to me that they executed the same for the uses and purposes therein set forth.

Seal

Patricia S. Keith
Notary Public

PATRICIA S. KEITH
NOTARY PUBLIC, IN AND FOR
STATE OF TEXAS
COMMISSION EXPIRES JULY 20, 1987

Case Docket No.: 509-020

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of
Rajni JANI and Robert Gregg HARRIS

Serial Number:

Filed: October 31, 1984

For: SUSTAINED RELEASE, COMFORT FORMULATION FOR GLAUCOMA THERAPY

RECORDING OF ASSIGNMENT

Honorable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Sir:

It is respectfully requested that the attached Assignment

From: Rajni JANI and Robert Gregg HARRIS

To: ALCON LABORATORIES, INC.

be recorded in the U.S. Patent and Trademark Office.

Please forward the recorded Assignment to:

Robert L. Price
LOWE, KING, PRICE & BECKER
2001 Jefferson Davis Hwy.
Arlington, VA 22202

The $20.00 recording fee is attached.

Respectfully submitted,

LOWE, KING, PRICE & BECKER

Robert L. Price
Registration No. 22,685

2001 Jefferson Davis Hwy.
Arlington, VA 22202
(703) 521-6633

APPENDIX B

A copy of page 415 from USP Dictionay of USAN and International Drug Names

The authorized list of established names for drugs in the United States of America

USP Dictionary

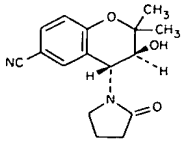
of USAN and International Drug Names

1998

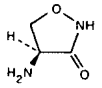
Published in accordance with the directions of the Nomenclature Committee of the USP Committee of Revision, with the cooperation of the United States Adopted Names Council

U.S. Pharmacopeia
12601 Twinbrook Parkway, Rockville, MD 20852

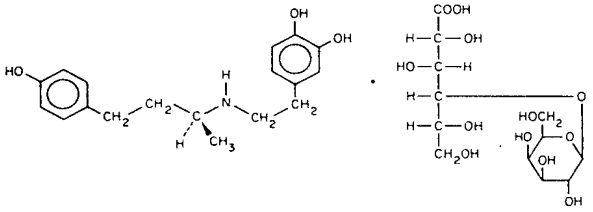
Anti-asthmatic; antihypertensive. (SmithKline Beecham) ✧*BRL-38227*



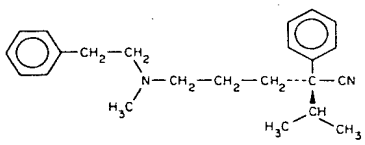
Levcycloserine [*1990*] (lev′ sye kloe ser een). $C_3H_6N_2O_2$. 102.09. (1) 3-Isoxazolidinone, 4-amino-, (*S*)-; (2) (*S*)-4-Amino-3-isoxazolidinone. *CAS-339-72-0.* INN. *Enzyme inhibitor (Gaucher's disease).*



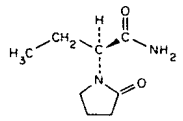
Levdobutamine Lactobionate [*1991*] (lev doe byoo′ ta meen). $C_{18}H_{23}NO_3.C_{12}H_{22}O_{12}$. 659.69. [Levdobutamine is INN.] (1) 1,2-Benzenediol, 4-[2-[[3-(4-hydroxyphenyl)-1-methylpropyl]amino]ethyl]-, (*S*)-, 4-*O*-β-D-galactopyranosyl-D-gluconate (salt); (2) 4-[2-[[(*S*)-3-(*p*-Hydroxyphenyl)-1-methylpropyl]amino]ethyl]pyrocatechol lactobionate (1:1) (salt). *CAS-129388-07-4; CAS-61661-06-1* [levdobutamine]. *Cardiotonic.* (Lilly†) ✧*LY206243 lactobionate*



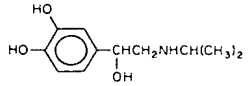
Levemopamil. $C_{23}H_{30}N_2$. 334.51. (−)-(*S*)-2-Isopropyl-5-(methylphenethylamino)-2-phenylvaleronitrile. *CAS-101238-51-1.* INN.



Levetiracetam. $C_8H_{14}N_2O_2$. 170.21. (*S*)-α-Ethyl-2-oxo-1-pyrrolidineacetamide. *CAS-102767-28-2.* INN.



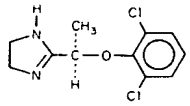
Levisoprenaline. $C_{11}H_{17}NO_3$. 211.26. (−)-α-(Isopropylaminomethyl)protocatechuyl alcohol. *CAS-51-31-0.* INN; DCF.



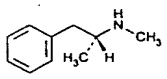
Levlen. Berlex brand of combination product; *See* Ethinyl Estradiol; Levonorgestrel.

† Brand name formerly used, and/or firm no longer concerned with this product.

Levlofexidine. $C_{11}H_{12}Cl_2N_2O$. 259.14. (−)-(*R*)-2-[1-(2,6-Dichlorophenoxy)ethyl]-2-imidazoline. *CAS-81447-78-1.* INN.



Levmetamfetamine (lev met am fet′ a meen). **USP.** $C_{10}H_{15}N$. 149.24. (1) Benzeneethanamine, *N*,α-dimethyl-, (*R*)-; (2) (−)-(*R*)-*N*, α-Dimethylphenethylamine. *CAS-33817-09-03. Nasal decongestant.*

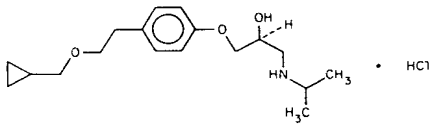


levo-BC-2605. Code designation for Oxilorphan.

levo-BC-2627. Code designation for Butorphanol.

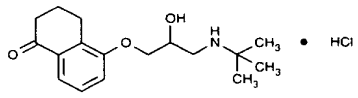
levo-BC-2627 tartrate. Code designation for Butorphanol Tartrate.

Levobetaxolol Hydrochloride [*1989*] (lee voe be tax′ oh lol). $C_{18}H_{29}NO_3.HCl$. 343.90. [Levobetaxolol is INN.] (1) 2-Propanol, 1-[4-[2-(cyclopropylmethoxy)ethyl]phenoxy]-3-[(1-methylethyl)amino]-, hydrochloride, (*S*)-; (2) (−)-(*S*)-1-[*p*-[2-(Cyclopropylmethoxy)ethyl]phenoxy]-3-(isopropylamino)-2-propanol hydrochloride. *CAS-116209-55-3; CAS-93221-48-8* [levobetaxolol]. *Anti-adrenergic (β-receptor).* (Synthelabo Pharmacie, France) ✧*AL1577A*

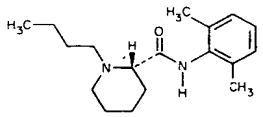


levo-BL-4566. Code designation for Moxazocine.

Levobunolol Hydrochloride [*1979*] (lee voe byoo′ noe lole). **USP.** $C_{17}H_{25}NO_3.HCl$. 327.85. [Levobunolol is INN and BAN.] (1) 1(2*H*)-Naphthalenone, 5-[3-[(1,1-dimethylethyl)amino]-2-hydroxypropoxy]-3,4-dihydro-, hydrochloride, (−)-; (2) (−)-5-[3-(*tert*-Butylamino)-2-hydroxypropoxy]-3,4-dihydro-1(2*H*)-naphthalenone hydrochloride. *CAS-27912-14-7; CAS-47141-42-4* [levobunolol]. *Anti-adrenergic (β-receptor).* Betagan (Allergan) ✧*W 7000A*



Levobupivacaine. $C_{18}H_{28}N_2O$. 288.44. (*S*)-1-Butyl-2′,6′-pipecoloxylidide. *CAS-27262-47-1.* INN; BAN.



Levocabastine Hydrochloride [*1985*] (lee′ voe kab as teen). $C_{26}H_{29}FN_2O_2.HCl$. 456.99. [Levocabastine is INN and BAN.] (1) 4-Piperidinecarboxylic acid, 1-[4-cyano-4-(4-fluorophenyl)cyclohexyl]-3-methyl-4-phenyl-, monohydrochloride, (−)-[1(*cis*),3α,4β]-; (2) (−)-*trans*-1-[*cis*-4-Cyano-4-(*p*-fluorophenyl)cyclohexyl]-3-methyl-4-phenylisonipecotic acid monohydrochloride. *CAS-79547-78-7; CAS-79516-68-0* [levocabastine]. *Antihistaminic.* (Janssen Phar-

APPENDIX C

A copy of the FDA-approved package insert for the approved product

2/17/00
approved 2/23/00

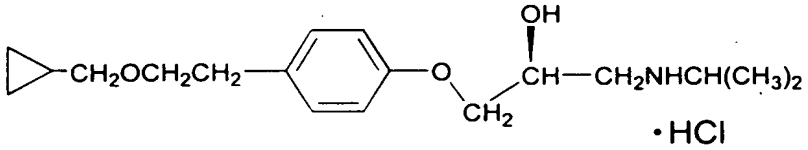
FINAL PACKAGE INSERT TEXT

BETAXON™
(levobetaxolol hydrochloride ophthalmic suspension)
0.5% as base

DESCRIPTION: BETAXON™ (levobetaxolol hydrochloride ophthalmic suspension) 0.5% contains levobetaxolol hydrochloride, a cardioselective beta-adrenergic receptor blocking agent, in a sterile resin suspension formulation. Levobetaxolol hydrochloride is a white, crystalline powder with a molecular weight of 343.89. The specific rotation is:

$$[\alpha]_{589nm}^{25°C} -19.67° \text{ (c=20 mg/mL; methanol).}$$

The chemical structure is:



Empirical Formula: $C_{18}H_{29}NO_3 \bullet HCl$

Chemical Name:

(S)-1-[p-[2-(cyclopropylmethoxy)ethyl]phenoxy]-3-(isopropylamino)-2-propanol hydrochloride.

Each mL of BETAXON™ (levobetaxolol hydrochloride ophthalmic suspension) 0.5% contains: **Active:** levobetaxolol HCl 5.6 mg equivalent to 5.0 mg of levobetaxolol free base. **Preservative:** benzalkonium chloride 0.01%. **Inactives:** mannitol, poly(styrene-divinyl benzene) sulfonic acid, Carbomer 974P, boric acid, N-lauroylsarcosine, edetate disodium, hydrochloric acid or tromethamine (to adjust pH) and purified water. It has a pH of 5.5 to 7.5 and an osmolality of 260 to 340 mOsm per kg.

CLINICAL PHARMACOLOGY: Levobetaxolol is a cardioselective (beta-1-adrenergic) receptor blocking agent that does not have significant membrane-stabilizing (local anesthetic) activity and is devoid of intrinsic sympathomimetic action. Animal studies suggest levobetaxolol (S-isomer) is the more active enantiomer of betaxolol (racemate).

When instilled in the eye, BETAXON™ Ophthalmic Suspension has the action of reducing elevated intraocular pressure. Elevated IOP presents a major risk factor in glaucomatous field loss. The higher the level of IOP, the greater the likelihood of optic nerve damage and visual field loss. In two well-controlled clinical studies in which a total of 356 patients were dosed for three months, BETAXON Ophthalmic Suspension produced clinically relevant reductions in IOP at all follow-up visits. At 8 AM after nighttime dosing (trough), IOP was reduced from baseline approximately 4 to 5 mmHg (16% to 21%). At 10 AM, two hours after dosing (peak), IOP was reduced from baseline approximately 5 to 6 mmHg (20% to 23%).

Since racemic betaxolol and other beta-adrenergic antagonists have been shown to reduce intraocular pressure by a reduction of aqueous production as demonstrated by tonography and aqueous fluorophotometry, it is assumed that the mechanism of action of levobetaxolol is similar. The intraocular lowering effect of racemic betaxolol can generally be noted within 30 minutes and the maximal effect can usually be detected two hours after topical administration. It is assumed that the intraocular lowering time profile of levobetaxolol is similar. A single dose provides approximately a 12-hour reduction in intraocular pressure.

BETAXON Ophthalmic Suspension 0.5% (levobetaxolol hydrochloride ophthalmic suspension) was dosed topically for 7 days to steady-state in 20 normal volunteers. An average maximal levobetaxolol plasma concentration (Cmax) of 0.5 ± 0.14 ng/mL was reached about three hours after the last dose. The mean half-life of levobetaxolol was approximately 20 hours.

In comparisons between BETAXON™ Ophthalmic Suspension and non-cardioselective beta blockers in reactive airway subjects, BETAXON™ Ophthalmic Suspension is expected to demonstrate less effect on pulmonary function [FEV_1 and Forced Vital Capacity (FVC)].

The cardiovascular effects of BETAXON™ ophthalmic suspension 0.5% and betaxolol ophthalmic solution 1% were compared in double-masked, crossover studies to timolol maleate ophthalmic solution 0.5%. Levobetaxolol and betaxolol were shown during exercise to have significantly less effect on heart rate and systolic blood pressure than timolol maleate.

INDICATIONS AND USAGE: BETAXON™ (levobetaxolol hydrochloride ophthalmic suspension) 0.5% is indicated for lowering intraocular pressure in patients with chronic open-angle glaucoma or ocular hypertension.

CONTRAINDICATIONS: Hypersensitivity to any component of this product. BETAXON™ Ophthalmic Suspension is contraindicated in patients with sinus bradycardia, greater than a first degree atrioventricular block, cardiogenic shock, or patients with overt cardiac failure.

WARNING: Topically applied beta-adrenergic blocking agents may be absorbed systemically. The same adverse reactions found with systemic administration of beta-adrenergic blocking agents may occur with topical administration. For example, severe respiratory reactions and cardiac reactions, including death due to bronchospasm in patients with asthma, and rarely death in association with cardiac failure, have been reported with topical application of beta-adrenergic blocking agents.

BETAXON™ Ophthalmic Suspension has been shown to have a minor effect on heart rate and blood pressure in clinical studies. Caution should be used in treating patients with a history of cardiac failure or heart block. Treatment with BETAXON™ Ophthalmic Suspension should be discontinued at the first signs of cardiac failure.

PRECAUTIONS:

General:

Diabetes Mellitus. Beta-adrenergic blocking agents should be administered with caution in patients subject to spontaneous hypoglycemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic receptor blocking agents may mask the signs and symptoms of acute hypoglycemia.

Thyrotoxicosis. Beta-adrenergic blocking agents may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-adrenergic blocking agents, which might precipitate a thyroid storm.

Muscle Weakness. Beta-adrenergic blockade has been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (e.g., diplopia, ptosis and generalized weakness).

Major Surgery. Consideration should be given to the gradual withdrawal of beta-adrenergic blocking agents prior to general anesthesia because of the reduced ability of the heart to respond to beta-adrenergically mediated sympathetic reflex stimuli.

Pulmonary. Caution should be exercised in the treatment of glaucoma patients with excessive restriction of pulmonary function. There have been reports of asthmatic attacks and pulmonary distress during betaxolol treatment. Although rechallenges of some such patients with ophthalmic betaxolol has not adversely affected pulmonary function test results, the possibility of adverse pulmonary effects in patients sensitive to beta blockers cannot be ruled out.

Information for Patients: Do not touch dropper tip to any surface, as this may contaminate the contents. Do not use with contact lenses in eyes.

Drug Interactions: Patients who are receiving a beta-adrenergic blocking agent orally and BETAXON™ Ophthalmic Suspension should be observed for a potential additive effect either on the intraocular pressure or on the known systemic effects of beta blockade.

Close observation of the patient is recommended when a beta blocker is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or bradycardia.

Levobetaxolol is an adrenergic blocking agent; therefore, caution should be exercised in patients using concomitant adrenergic psychotropic drugs.

Risk from anaphylactic reaction: While taking beta-blockers, patients with a history of atopy or a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated accidental, diagnostic, or therapeutic challenge with such allergens. Such patients may be unresponsive to the usual doses of epinephrine used to treat anaphylactic reactions.

Ocular: In patients with angle-closure glaucoma, the immediate treatment objective is to reopen the angle by constriction of the pupil with a miotic agent. Racemic betaxolol has little or no effect on the pupil. It is expected that levobetaxolol will also have little or no effect on the pupil. When BETAXON™ Ophthalmic Suspension is used to reduce elevated intraocular pressure in angle-closure glaucoma, it should be used with a miotic and not alone.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In lifetime studies in mice at oral doses of 6, 20 and 60 mg/kg/day and in rats at oral doses of 3, 12 and 48 mg/kg/day, betaxolol HCl demonstrated no carcinogenic effect. Higher dose levels were not tested. Levobetaxolol was not mutagenic in the Ames assay, chromosomal aberration, mouse lymphoma, and cell transformation assays *in vitro*. Levobetaxolol demonstrated potential mutagenicity in the sister chromatid exchange assay in Chinese Hamster Ovarian cell *in vitro* in the presence of metabolic activation systems.

Pregnancy: Pregnancy Category C. Reproduction, teratology, and peri- and postnatal studies have been conducted with orally administered betaxolol HCl and levobetaxolol HCl in rats and rabbits. There was evidence of drug related postimplantation loss in rabbits with levobetaxolol HCl at 12 mg/kg/day and sternebrae malformations at 4 mg/kg/day. No other adverse effects on reproduction were noted at subtoxic dose levels. There are no adequate and well-controlled studies in pregnant women. BETAXON Ophthalmic Suspension should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether BETAXON Ophthalmic Suspension is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when BETAXON Ophthalmic Suspension is administered to nursing women.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

Geriatric Use: No overall differences in safety or effectiveness have been observed between elderly and other adult patients.

ADVERSE REACTIONS:

Ocular: In clinical trials, the most frequent event associated with the use of BETAXON™ Ophthalmic Suspension 0.5% has been transient ocular discomfort upon instillation (11%). Transient blurred vision has been reported in approximately 2% of patients. Other ocular events have been reported in less than 2% of patients and include: cataracts, and vitreous disorders. All other ocular events occurred one time at an incidence of less than 0.2%.

Systemic: Systemic reactions following administration of BETAXON Ophthalmic Suspension 0.5% and other topical ocular formulations of betaxolol have been at an incidence of less than 2%. These include:

Cardiovascular: Bradycardia, heart block, hypertension, hypotension, tachycardia, and vascular anomaly

Central Nervous System: Anxiety, dizziness, hypertonia, and vertigo.

Digestive: Constipation and dyspepsia.

Endocrine: Diabetes and hypothyroidism.

Metabolic and Nutritional Disorders: Gout, hypercholesteremia, and hyperlipidemia.

Musculoskelatal: Arthritis and tendonitis.

Pulmonary: Pulmonary distress characterized by bronchitis, dyspnea, pharyngitis, pneumonia, rhinitis, and sinusitis.

Skin and Appendages: Alopecia, dermatitis, and psoriasis.
Special Senses: Ear pain, otitis media, taste perversion, and tinnitus.
Urogenital: Breast abscess and cystitis.
Other: Accidental injury, headache, and infection.

OVERDOSAGE: No information is available on overdosage in humans. The oral maximum tolerated dose (MTD) of levobetaxolol in rats was 1250 mg/kg. The symptoms which might be expected with an overdose of a systemically administered beta-1-adrenergic receptor blocking agent are bradycardia, hypotension and acute cardiac failure.

DOSAGE AND ADMINISTRATION: The recommended dose is one drop of BETAXON™ (levobetaxolol hydrochloride ophthalmic suspension) 0.5% in the affected eye(s) twice daily. In some patients, the intraocular pressure lowering responses to BETAXON™ Ophthalmic Suspension may require a few weeks to stabilize. As with any new medication, careful monitoring of patients is advised. The concomitant use of two topical beta-adrenergic agents is not recommended.

HOW SUPPLIED: BETAXON™ (levobetaxolol hydrochloride ophthalmic suspension) 0.5% is supplied as follows: 5, 10 and 15 mL in a clear LDPE plastic ophthalmic DROP-TAINER® dispenser and a yellow polypropylene screw cap.

5 mL: NDC 0065-0239-05
10 mL: NDC 0065-0239-10
15 mL: NDC 0065-0239-15

STORAGE: Store upright 39°F to 77°F (4°C to 25°C).
Protect from light.
Shake well before using.

Rx Only

U.S. Patent Nos. 4,911,920; 5,520,920; 5,540,918; 4,342,783; 4,252,984 and Pat. Pending.

Alcon® OPHTHALMIC *(logo)*
ALCON LABORATORIES, INC.
Fort Worth, Texas 76134 USA

APPENDIX D

FDA Approval Letter of February 23, 2000

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-114 FEB 23 2000

Alcon Research, Ltd.
Attention: Scott Krueger
Senior Director, Regulatory Affairs
6201 South Freeway
Fort Worth, Texas 76134-2099

Dear Mr. Krueger:

Please refer to Alcon Universal, Limited's new drug application (NDA) dated August 25, 1999, received August 26, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Betaxon (levobetaxolol hydrochloride ophthalmic suspension) 0.5%.

We acknowledge receipt of your submissions dated May 25 and 26, October 1, 15 and 20, December 2, 7, 8, 13, 17, and 20, 1999, and January 12, 18 and 24, and February 15 and 17, 2000.

This new drug application provides for the use of Betaxon for lowering intraocular pressure in patients with chronic open-angle glaucoma or ocular hypertension.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submission dated February 17, 2000. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft labeling submitted February 17, 2000. Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "**FPL for approved NDA 21-114.**" Approval of this submission by FDA is not required before the labeling is used.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We note that you have not fulfilled the requirements of 21 CFR 314.55 (or 601.27). We are deferring submission of your pediatric studies until October 1, 2002. However, in the interim, please submit your pediatric drug development plans and we will review your plans.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). A written request for pediatric information on levobetaxolol hydrochloride for the treatment of elevated intraocular pressure was issued on October 15, 1999. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Lori M. Gorski, Project Manager, at (301) 827-2090.

Sincerely,

Wiley A. Chambers, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic and
Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

APPENDIX E

A cut-up copy of United States Patent 4,911,920

United States Patent [19]

Jani et al.

[11] **Patent Number: 4,911,920**

[45] **Date of Patent: Mar. 27, 1990**

[54] **SUSTAINED RELEASE, COMFORT FORMULATION FOR GLAUCOMA THERAPY**

[75] Inventors: **Rajni Jani; Robert G. Harris**, both of Fort Worth, Tex.

[73] Assignee: **Alcon Laboratories, Inc.**, Fort Worth, Tex.

[21] Appl. No.: **154,514**

[22] Filed: **Feb. 5, 1988**

Related U.S. Application Data

[63] Continuation of Ser. No. 890,519, Jul. 30, 1986, abandoned, which is a continuation of Ser. No. 667,003, Oct. 31, 1984, abandoned.

[51] **Int. Cl.**[4] **A61K 31/78**

[52] **U.S. Cl.** **424/78**; 424/81; 514/913

[58] **Field of Search** 514/913; 424/19, 78, 424/81

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,867,519	2/1975	Michaels	424/19
3,962,414	6/1976	Michaels	424/19

3,987,163	10/1976	Rankin	424/78
4,127,674	11/1978	Leopold	424/324
4,207,890	6/1980	Mamajek et al	128/223
4,271,143	6/1981	Schoenwald et al.	424/78
4,407,792	10/1983	Schoenwald et al.	424/81
4,462,982	7/1984	Samejima et al.	429/19
4,521,414	6/1985	Chion et al.	514/229

OTHER PUBLICATIONS

Chem. Abst. 98:210936j (1983) Heath et al.

Primary Examiner—Shep K. Rose
Assistant Examiner—Zohyeh A. Fay
Attorney, Agent, or Firm—James A. Arno; Gregg C. Brown; Sally Yeager

[57] **ABSTRACT**

Disclosed are nonstinging, sustained release ophthalmic formulations to control intraocular pressure in anti-glaucoma therapy comprising a basic active, a cation exchange resin, and, inter alia, an acidic, mucomimetic polymer. Also disclosed are methods of treatment comprising administering such formulations topically to the eye when indicated for control and lowering of intraocular pressure.

12 Claims, No Drawings

SUSTAINED RELEASE, COMFORT FORMULATION FOR GLAUCOMA THERAPY

This is a continuation, of application Ser. No. 890,519 which is a continuation of application Ser. No. 667,003 both abandoned.

BACKGROUND OF THE INVENTION

This invention relates to ophthalmic formulations useful in controlling and lowering intraocular pressure (IOP) in the treatment of glaucoma. The formulations of the present invention are characterized as long lasting (sustained release) and are initially and continually comfortable to the eye. Specifically, the invention relates to formulations of the above characteristics which comprise, inter alia, a basic active and a cationic exchange resin (finely divided) dispersed in an aqueous solution or gel of an acidic, mucomimetic polymer. Such resulting aqueous gel or pourable liquid formulations are characterized by controlled cationic-anionic interactions, which appear to be responsible for the resulting comfort and sustained release properties. This invention also relates to methods of treatment which comprise administering the described compositions when indicated for treating ocular hypertension and glaucoma.

The term "basic active" means the active ingredient or ingredients in the disclosed formulations which have the desired effect on intraocular pressure and which bear, or are capable of bearing, a positive charge during formulation of the final product or as formulated in the final product form. Thus, the term basic, or cationic, active is descriptive for purposes of the disclosure and claims.

Such basic actives include all presently known beta blockers which demonstrate the requisite cationic charge and IOP effect. Typically, such beta blockers are represented by the following generic structure, which structure also represents the beta blocker basic actives of the present disclosure:

$$R^1—O—CH_2—CH(OH)—CH_2—NR^2R^3 \quad (I)$$

wherein:

R^1 is a substituted or unsubstituted cyclic or aliphatic moiety; cyclic moieties include mono- and polycyclic structures which may contain one or more heteroatoms selected from C, N, and O; R^2 and R^3 are independently selected from H and substituted and unsubstituted alkyl. With regard to Structure (I), above, the following references are incorporated herein by reference: *Annular Reports in Medicinal Chemistry* 14, 81–87 (1979); *J. Med. Chem.* 1983, 26,1570–1576; *ibid.*, 1984, 27, 503–509; *ibid.*, 1983, 26, 7–11; *ibid.*, 1983, 26, 1561–1569; *ibid.*, 1983, 1109–1112; *ibid.*, 1983, 26, 950–957; *ibid.*, 1983, 26, 649–657; and *ibid.*, 1983, 26, 352–357. Representative of such basic actives are: betaxolol, timolol, befunolol, labetalol, propanolol, bupranolol, metaprolol, bunalol, esmalol, pindolol, carteolol, hepunolol, metipranolol, celiprolol, azotinolol (S-596), diacetolol, acebutolol, salbutamol, atenulol, isoxaprolol, and the like.

The definition of basic active also includes the following classes of drugs which are used in treatment of ocular hypertension and glaucoma: pilocarpine; epiniphrine; proepinephrine; norepinephrine; pronorepi-

nephrine; clonidine; and clonidine derivatives, for example, p-aminoclonidine and p-acetoamidoclonidine.

Thus, in summary, the basic active component of the present invention is defined by its intraocular pressure lowering effect or static control thereof, and by its cationic nature in an aqueous medium in the pH range of from 3.0 to 8.5. The following patent publications, which are incorporated herein by reference, further representatively demonstrate the basic actives of the present invention: U.S. Pat. Nos. 4,252,984; 3,309,406; 3,619,370; 3,655,663; 3,657,237; 4,012,444; 3,663,607; 3,836,671; 3,857,952; 3,202,660; and 2,774,789.

DETAILED DESCRIPTION OF THE INVENTION

The ophthalmic formulations of the present invention are in the form of: anhydrous salts; pourable, aqueous dispersions; and aqueous gels. The formulations comprise, in addition to conventional ingredients which provide, for example, bacteriostatic and formulatory balance functions, a critical polyanionic polymer, a cation exchange resin and the basic active of choice. Such anhydrous salt forms are incorporated into ointments or solid ocular inserts which form colloidal gels in situ on administration to the eye. The pourable liquid and gel embodiments are applied topically to the eye. It should be noted that such liquid and gel embodiments can be obtained from the anhydrous form on formulation with water.

The formulations of the present invention demonstrate sustained release of the basic active and are comfortable on topical administration to the eye. It should be noted, in general sense, that a stinging sensation results when the basic actives, identified above, are administered neat. Thus, achieving both comfort and sustained release in an unexpected result and permits administration of a class of compounds that otherwise might not be considered.

Polyanionic Polymer Component

The high molecular weight, polyanionic polymers useful in the present invention have a molecular weight of from about 50,000 to about 6 million. The polymers are characterized as having carboxylic acid functional groups, and preferably contain from 2 to 7 carbon atoms per functional group. The gels which form during the preparation of the ophthalmic polymer dispersion have a viscosity of from about 1,000 to about 300,000 cps. In addition to the basic active-polymer (anioniccationic) interactions, mentioned above, the high molecular weight polymers used in the compositions of the present invention thicken the compositions to provide a gel, and provide a special type of rheology, i.e., plastic viscosity, which is translatable to the sustained release and comfort of the final compositions. Such compositions range in pH from 3.0 to 8.5.

The pourable liquid embodiments (administered as drops to the eye) of the present invention have a viscosity of from about 1 to 20,000 cps. The pH requirements are the same as recited above for the gel final products, i.e., pH 3.0–8.5.

The third pharmaceutical form of the present invention, the anhydrous salt form, is derived from a salt of the polycarboxylic acid polymer and the basic active. (The presence of the cationic ion exchange resin also contributes to salt formation; the nature of the ion exchange resin, in all embodiments of the present invention is defined below.) Such salts can be formulated, or reconstituted, to aqueous gels and pourable dispersions,

as described above, on addition of water; or can be formulated as ocular inserts according to known technology and shapes; or they can be combined with an oleaginous vehicle to form an ophthalmic ointment. All such final ophthalmic pharmaceutical forms are fully described below.

The term "plastic viscosity", above, is indicative of a material that does not perceptibly flow until a certain force or stress value is exceeded; this force or stress is referred to as the yield value. While not wishing to be bound by any theory, it is believed that the increased duration of activity of the compositions of the present invention is related, in part, to the yield value. The compositions of the present invention exhibit a unique response to shear stress. When the yield value is exceeded, the gel structure is altered temporarily, allowing the gel to flow. In the eye, this mechanism is partially attributable to the blinking eyelid. When the stress is removed (eyelid at rest), the structure of the gel is partially re-established. Other factors which explain the duration of the formulations of the present invention are related to ionic interactions, and a release mechanism which is explained by a dynamic equilibrium involving normal tear production and the displacement of basic active cations by cations present in tears. This mechanism is mentioned again, below.

Suitable polymers useful in the present invention are carboxyl vinyl polymers. Preferred polymers of this class include the so called Carbomers, available under the trade name Carbopol from the B. F. Goodrich Company; and ethylene maleic anhydride polymeric material, available under the trade name EMA from the Monsanto Company. The known and readily available polymers Carbopol 934 and 940 are specifically preferred. The polymers are used in the aqueous gel compositions at a level up to about 8% by weight; pourable liquid compositions comprise 0.05% to 2.0% by weight polymer.

Basic Active

The preferred basic actives of the present invention are those disclosed above. The most preferred basic actives are betaxolol and timolol. The basic active, in the gel and pourable liquid embodiments, is present at a level of from about 0.01 to 4.0 wt. %; the most preferred range is from 0.10 to 1.0 wt. %.

Ion Exchange Resin

The cationic resin component of the formulations of the present invention provides an additional means of sustained release of the basic active, and appears to be necessary for initial and prolonged comfort. Such resins are characterized as either strongly acidic such as those having sulfonic acid functionality, or weakly acidic cation exchangers such as those having carboxylic acid functionality. The resin must be incorporated as a finely divided powder, that is, 95% of the resulting spheroidal particles must have a diameter less than 20.0 microns. The release of the basic active held by the cation exchange resin and the anionic polymer is achieved when ions naturally present in the tear fluid, principally sodium and potassium, compete with the bound basic active for sites on the polymer vehicle and the ion exchange resin. Thus released, the basic active is presented to the eye surface for transport to the receptor sites.

Any pharmaceutical grade cationic ion exchange resin is suitable for the formulation, and they can be used either in the hydrogen form or in the sodium form. Such resins are readily available, for example, from

Rohm & Haas under the "Amberlite" tradename and from Dow Chemical Co. under the "Dowex" tradename.

The ion exchange resin component is present in the formulations of the present invention at a level of from 0.05% to 10.0% by weight. The average particle size diameter of the resin ranges from 1 to 20 microns.

The particle size of the resin is critical, both with respect to mode of action and comfort. Typically the average particle size of the commercially available form of the ion exchange material of choice is about 40 to 150 microns. Such particles are most conveniently reduced to a particle size range of about 1.0 to 25 microns by ball milling according to known techniques.

Other Ingredients

Antimicrobial Preservative:

Ophthalmic products are typically packaged in multidose form. Preservatives are thus required to prevent microbial contamination during use. Suitable preservatives include: benzalkonium chloride, thimerosal, chlorobutanol, methyl paraben, propyl paraben, phenylethyl alcohol, edetate disodium, sorbic acid, Onamer M, or other agents known to those skilled in the art. Typically such preservatives are employed at a level of from 0.001% to 1.0% by weight.

Tonicity Agents:

The tonicity, or osmolality, of the product can be adjusted to either hypotonicity, iotonicity or hypertonicity relative to normal tears by use of conventional materials known to the art. Such tonicity agents, however are limited to nonionic compounds and typically, when employed, range from 0.0% to 10% weight percent in the final product. Nonionic agents representatively include: mannitol, dextrose, glycerine and propyleneglycol; their presence in the final product form, however, is optional.

Formulation

The compositions are formulated in three basic states: 1. gels; 2. pourable liquids; and 3. anhydrous salts:

1. Gels

The cationic exchange resin component is dispersed in water. The basic active component is then added with stirring. The polyanionic polymer component is then added. The resulting product has a viscosity ranging from 1000 to 300,000 cps depending on the anionic polymer concentration. The resulting pH is 3.0 to 8.5, which may be adjusted, if necessary, with HCl or NaOH.

2. Pourable Liquids

The cationic exchange resin component is dispersed in 10 to 50 vol. percent of total water taken in formulation, and then basic active is dispersed and/or dissolved with stirring. The polyanionic polymer, as an aqueous dispersion, is added until the desired pH of the product is obtained. The pH of the product can be adjusted to the desired value by varying basic active/polymer/resin ratio. If desired, final pH of product can be adjusted with addition of either NaOH or HCl. The preferred pH range for ophthalmic formulations is from 3.0 to 8.5. The final product is a dispersion, which may require high energy mixing to break any agglomeration to achieve uniformity. Other formulation ingredients are then added with mixing. The resulting product has a viscosity ranging from 1.0 to 20,000 cps depending on the anionic polymer concentration.

3. Anhydrous Salts

The basic active, the ion exchange resin, and the polyanionic polymer are combined in water and, following mixing, are lyophilized to a powder. Fillers like mannitol and other materials may be added to facilitate the freeze/drying process according to techniques well known to those skilled in the art. The anhydrous salts produced in this manner an then be formulated or reconstituted to aqueous gels and liquids, or can be formulated and shaped as ocular inserts. The lyophilized powder can also be combined with a nonaqueous vehicle to form an ophthalmic ointment.

Such anhydrous salt embodiments of the present invention can also be prepared by extracting the initial aqueous dispersion with an organic solvent such as ethanol, chloroform, benzene, or the like, and evaporating the organic solvent to produce the desired salt complex. The resulting product is substantially equivalent to the above-described lyophilized product.

Utility

The Ophthalmic formulations of the present invention are administered to the eyes as gels, pourable liquids (eye drops), and in the form of ointments and ocular inserts; the latter classifications are formulated from anhydrous salts. All such compositions are formulated to control the release of basic active upon administration to the eye and thereby provide a sustained release effect. Typically such administration is necessary once or twice per day. The precise dosage regiment is left to the routine discretion of the clinician.

The following examples illustrate, but do not limited the compositional or method of treatment aspects of the present invention.

EXAMPLE 1

Preparation of Betaxolol Free Base from Betaxolol Hydrochloride

Betaxolol Hydrochloride is disclosed in U.S. Pat. No. 4,252,984, and is commercially available.

Betaxolol Hydrochloride (0.88 moles) is dissolved in water and the solution is chilled in an ice-bath. To this solution is added a solution of sodium hydroxide (0.97 moles) in water portionwise to make the mixture basic while it is stirred vigorously. At this point the pH of the mixture is approximately 9.6. The resulting white solid is collected by filtration and washed with a large volume of water.

After press/drying in the filter funnel, the semi-dry solid is resuspended in a large volume of water and stirred for 1-2 hours. The white solid is collected by filtration and washed with a large volume of water to afford salt-free Betaxolol free base, which is dried in vacuo.

EXAMPLE 2

Example 2

	Product Composition		
	A (wt %)	B (wt %)	C (wt %)
Betaxolol	0.50	0.25	1.0
CARBOPOL-934 P (Carbomer)	0.25	0.15	0.35
Sodium Poly(Styrene-Divinyl Benzene) Sulfonate	0.25	0.125	0.50
Benzalkonium Chloride	0.01	0.01	0.01
Mannitol	5.0	5.0	5.0

-continued

Example 2	Product Composition		
	A (wt %)	B (wt %)	C (wt %)
Water	To Make 100%		

Procedure

Finely divided Amberlite IRP-69 resin, a sodium poly(styrenedivinyl benzene) sulfonate, and the betaxolol are mixed in 50% of the total water volume component to form a uniform dispersion. The Carbopol-934P is added slowly as an aqueous dispersion. The mixture is homogenized at high speed. The other ingredients are added as aqueous solutions. The final volume is made on addition of water. The resultant products, A, B and C, are white uniform suspensions.

EXAMPLE 3

Example 3	Product Composition		
	A (wt %)	B (wt %)	C (wt %)
Betaxolol Base	0.50	0.25	1.0
Poly(Styrene-Divinyl Benzene) Sulfonic acid	0.25	0.125	0.5
Carbopol-934P	0.20	0.1	0.35
Benzalkonium Chloride	0.01	0.01	0.01
Mannitol	5.0	5.0	5.0
Water	To Make 100%		

Procedure

The solutions A, B and C of Example 3 are prepared following the procedure of Example 2. The resulting products are white to off-white uniform suspensions with pH between 5.5 to 6.5.

Following the procedure of Examples 2 and 3, substantially equivalent results are obtained when the betaxolol component is replaced by an equivalent amount of timolol, or by any of the previously identified beta blockers and other basic actives, respectively.

The invention has been described herein with reference to certain preferred embodiments. However, as obvious variations thereon will become apparent to those skilled in the art, the invention it not to be considered as limited thereto.

What is claimed is:

1. A sustained release ophthalmic pharmaceutical composition in the form of an aqueous gel, a pourable aqueous dispersion, or anhydrous salt, for controlling and lowering intraocular pressure comprising:

a therapeutically effective amount of betaxolol;

an amount of an anionic mucomimetic polymer having carboxylic acid functional groups which comprise from 2 to 7 carbon atoms per functional group and a molecular weight of from 50,000 to 6 million such that the composition in the form of an aqueous gel or pourable aqueous dispersion has a viscosity of about 1 to about 20,000 cps.; and sodium poly(styrenedivinylbenzene) sulfonic acid at a concentration of from about 0.05% to 10.0% by weight, the composition having a pH of from about 3.0 to 8.5.

2. The composition according to claim 1 wherein the composition is an aqueous dispersion.

3. A composition according to claim 1 wherein the betaxolol is present at a concentration of from about 0.01 to 4.0 wt.%.

4. A composition according to claim 1 wherein the anionic mucomimetic polymer comprises carbomer.

5. A composition according to claim 1 wherein the betaxolol is present at a concentration of about 0.25 wt.%, the anionic mucomimetic polymer is carbomer present at a concentration of about 0.20 wt.%, and the sulfonic acid is present at a concentration of about 0.25 wt.%.

6. The composition of claim 1 wherein the particulate cation exchange resin is in the form of a finely divided powder, said powder consisting of spheroidal particles.

7. A method of treatment for controlling and lowering intraocular pressure which comprises administering topically to the affected eye a pharmaceutical composition which includes:

a therapeutically effective amount of betaxolol;

an amount of an anionic mucomimetic polymer having carboxylic acid functional groups which comprise from 2 to 7 carbon atoms per functional group and a molecular weight of from 50,000 to 6 million such that the composition in the form of an aqueous gel or pourable aqueous dispersion has a viscosity

of about 1 to about 20,000 cps.; and sodium poly(styrene-divinylbenzene) sulfonic acid at a concentration of from about 0.05% to 10.0% by weight, the composition having a pH of from about 3.0 to 8.5.

8. The method according to claim 7 wherein the composition is an aqueous dispersion.

9. A method according to claim 7 wherein the betaxolol is present at a concentration of from about 0.01 to 4.0 wt.%.

10. A method according to claim 7 wherein the anionic mucomimetic polymer comprises carbomer.

11. A method according to claim 7 wherein the betaxolol is present at a concentration of about 0.25 wt.%, the anionic mucomimetic polymer is carbomer present at a concentration of about 0.20 wt.%, and the sodium poly(styrene-divinylbenzene) sulfonic acid is present at a concentration of about 0.25 wt.%.

12. The method of claim 7 wherein the particulate cation exchange resin is in the form of a finely divided powder, said powder consisting of spheroidal particles.

* * * * *

APPENDIX F

Maintenance Fee Statements

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
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Washington, D. C. 20231

0902 B

75N4/0728

JAMES A. ARNO
PATENT DEPARTMENT
ALCON LABORATORIES, INC.
6201 SOUTH FREEWAY
FORT WORTH, TX 76134

DATE MAILED
07/28/93

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If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

ITM NBR	PATENT NUMBER	FEE CDE	FEE AMOUNT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	4,911,920	183	930	----	07/154,514	03/27/90	02/05/88	04	NO	PAID

If the "status" column for a patent number listed above does not indicate "PAID" a code or an asterisk (*) will appear in the "status" column. Where an asterisk (*) appears, the codes are set out below by the related item number. An explanation of the codes indicated in the "status" column and as set out below by the related item number appears on the reverse of the maintenance fee statement.

ITM NBR	ATTY DKT NUMBER
1	509-020/S

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Name of person signing Mary S. Langley

Signature Mary S. Langley

APR 19 2000
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3 ☒ The Commissioner is hereby authorized to charge any deficiency in the payment of the required fee(s) or credit any overpayment to Deposit Account No. 01-0682.

*Information required by 37 CFR 1.366(c)(columns 1 & 5). *Information requested under 37 CFR 1.366(d)* (columns 2-4 & 6-9)

Item	Patent Number* 1	Fee Code 2	Maintenance Fee Amount 3	Surcharge Amount 4	U.S. Serial Number* 5 [08/555/555]	Patent Date 6 mm/dd/yy	Application Filing Date 7 mm/dd/yy	Payment Year 8	Small Entity? 9
1	4,911,920	183	930.00	-	07/154,514	03/27/90	02/05/88	4	No
2									
3									
4									
5									
6									
7									
8									
Sub-totals—Columns 3 & 4			930.00	-					
Total Payment			930.00						

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*Respectfully submitted:
Alcon Laboratories, Inc.
Sally S. Yeager, Reg. No. 31,757
Payor's name

Sally S. Yeager
Payor's signature

(817) 551-4031
Payor's telephone number

PAYOR'S NUMBER (if assigned) 004691

FEE ADDRESS Alcon Laboratories, Inc.
Patent Department
6201 South Freeway
Fort Worth, Texas 76134

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Instructions to Docket Clerk

The following papers have been filed:

MAINTENANCE FEE TRANSMITTAL FORM PTO-1536

Description of paper: _____

Name of Applicant: Jani, et al

Patent ~~Serial~~ No.: 4,911,920

Atty. File No.: 0902B

Sender's Initials: SSY/al

Title (New Cases): _____

UNITED STATES DEPARTMENT OF COMMERCE
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1	4,911,920	184	2050	----	07/154,514	03/27/90	02/05/88	08	NO	PAID

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004691

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ITEM NBR	PATENT NUMBER	FEE CDE	FEE AMT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	4,911,920	184	2050	----	07/154,514	03/27/90	02/05/88	08	NO	PAID

ITM NBR	ATTY DKT NUMBER
1	509-020/B 702E

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Name of person signing Mary S. Langley
Signature Mary S. Langley

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2. ☒ The Commissioner is hereby authorized to charge $2,050.00 to cover the payment of the fee(s) indicated below to Deposit Account No. 01-0682.
3. ☒ The Commissioner is hereby authorized to charge any deficiency in the payment of the required fee(s) or credit any overpayment to Deposit Account No. 01-0682.

Information required by 37 CFR 1.366(c)(columns 1 & 5). *Information requested under 37 CFR 1.366(d) (columns 2-4 & 6-9).*

Item	Patent Number* 1	Fee Code 2	Maintenance Fee Amount 3	Surcharge Amount 4	U.S. Serial Number* 5 [06/555/555]	Patent Date 6 mm/dd/yy	Application Filing Date 7 mm/dd/yy	Payment Year	Small Entity? 9
1	4,911,920	184	2,050.00	-	07/154,514	03/27/90	02/05/88	8	No
2									
3									
4									
5									
6									
7									
8									
	Sub-totals—Columns 3 & 4		2,050.00	-					
	Total Payment		2,050.00						

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*Respectfully submitted:

Alcon Laboratories, Inc., sally S. Yeager
(Payor's name) Reg. No. 32,757

Sally S. Yeager
(Payor's signature)

(817) 551-4031
(Payor's telephone number)

PAYOR'S NUMBER (if assigned) 004691

FEE ADDRESS Alcon Laboratories, Inc.
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6201 South Freeway
Fort Worth, Texas 76134-2099

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Instructions to Docket Clerk

The following papers have been filed:

MAINTENANCE FEE TRANSMITTAL FORM, PTO_1536

7-23-97

Description of paper:

Name of Applicant: Jani, et al.

Patent ~~Serial~~ No.: 4,911,920

Atty. File No.: 09028 **Sender's Initials:** SSY/sl

Title (New Cases):

Express Mail No. EL534529609US

DECLARATION

This Application is submitted pursuant to extension of the term of United States Patent No. 4,911,920. The undersigned, as agent for Alcon Laboratories, Inc. ("Alcon"), the owner of said patent, hereby declares:

THAT I am an attorney of record in connection with United States Patent No. 4,911,920 and am authorized to act on behalf of Alcon in patent matters;

THAT I have reviewed and understand the contents of the attached Application papers consisting of a 13 page Application, a Declaration, and Appendices A-F;

THAT I believe United States Patent No. 4,911,920 is subject to extension pursuant to 35 U.S.C. §156 and 37 C.F.R. §1.710;

THAT I believe an extension of 579 days is fully justified under 35 U.S.C. §156 and the applicable regulations;

THAT I believe United States Patent No. 4,911,920 meets the conditions for extension of the term of a patent, as set forth in 37 C.F.R. §1.720; and

THAT all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this Application and any extension of United States Patent No. 4,911,920.

ALCON LABORATORIES, INC.

Date: April 19, 2000

By: _____
Sally Yeager, Reg. 32,757

Patent Department
Alcon Laboratories, Inc.
6201 So. Freeway
Fort Worth, TX 76134-2099
(817) 551-4031

Attorney Docket No.: 902B-2

CERTIFICATION

I hereby certify that the attached papers are duplicates of the accompanying papers consisting of a 13 page document titled "APPLICATION FOR EXTENSION OF TERM UNDER 35 U.S.C. §156", a Declaration, and Appendices A-F.

April 19, 2000
Date

Sally Teager, Reg. No. 32,757